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(54) Title: PROCESS FOR PRODUCING MERCAPTOALKANESULFONATES AND PHOSPHONATES AND DERIVATIVES THEREOF

(57) Abstract

A two step single–pot process for producing dimesna ($NaSO_3$–$(CH_2)_2$–S–S–$(CH_2)_2$–SO_3Na) begins by reacting an ω–alkenesulfonate with a sulfide such as NaSH to yield mesna (HS–$(CH_2)_2$–SO_3Na). (This can be isolated or converted to a C_{1-4} thioalkyl ether thereof by reaction with sodium alkoxide and an alkyl halide). In the second step, mesna is oxidised *in situ* with oxygen gas to yield dimesna. Higher alkane homologues and analogous phosphonates are prepared similarly. When preparing a phosphonate analogue a haloalkanephosphonate is an alternative starting compound. The C_{1-4}–alkylene chain analogues of these compounds can be prepared similarly.

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PROCESS FOR PRODUCING MERCAPTOALKANESULFONATES AND PHOSPHONATES AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

This invention relates to a process for producing mercaptoalkanesulfonates and phosphonates and derivatives thereof, especially sodium 2-mercaptoethanesulfonate (mesna; $HS-CH_2CH_2SO_3Na$) and disodium 2,2'-(dithiobis)ethane sulfonate (dimesna; $NaSO_3CH_2CH_2-S-S-CH_2CH_2SO_3Na$).

BACKGROUND OF THE INVENTION

Compounds of the general formula (I): $R_1-S-(CH_2)_m-R_2$ wherein R_1 is hydrogen, C_{1-4}-alkyl or $R_2-(CH_2)_m-S-$ and R_2 is SO_3M or PO_3M_2 wherein M or each M independently is sodium, potassium or hydrogen and m is 2, 3 or 4, are useful *inter alia* as chemotherapeutic protective agents used to mitigate the toxicity of platinum complex antitumor drugs which are given to patients with certain types of cancer. Thus, dimesna can be co-administered with cisplatin (cis-diamminedichloroplatinum) to protect the body against nephrotoxicity, and both mesna and dimesna can be co-administered with carboplatin (cisdiammine-1,1-cyclobutanedicarboxylatoplatinum) to protect the body against myelosuppression. Mesna has also been used as a protective agent with other antitumor drugs e.g. ifosfamide, oxazaphosphorine and etoposide.

Mesna is auto-oxidized in the body to dimesna under mildly basic conditions and in the presence of oxygen species, such as those present in plasma.

The chief prior processes for synthesizing mesna and dimesna (and like mercaptans and disulfides) include the conversion of various alkanesulfonic acids into their respective mercaptan derivatives (such as mesna) and the subsequent oxidation of the mercaptans into their respective disulfides (such as dimesna) by use of iodine-containing reagents, such as iodate. These processes,

while efficient, required isolation procedures to be performed to isolate and purify the end products from the reagents used. These processes generated environmental pollutants, which required disposal and could not be carried out in a single reaction vessel.

SUMMARY OF THE INVENTION

The present invention avoids these disadvantages in the production of dimesna and provides a more convenient method of making various alkylthio-, mercapto- and dithiobis-alkanesulfonates and phosphonates.

The invention provides a process of making compounds of the general formula I, said process comprising

(1) reacting a compound of formula

$CH_2X\text{-}CHY\text{-}(CH_2)_n\text{-}R_2$ (II),

wherein

X and Y together complete an olefinic carbon-carbon double bond or, where R_2 is PO_3M_2, X can be halo and Y is then hydrogen;

n is 0, 1 or 2; and

R_2 is as defined above, with a sulfide of the general formula Z-SH, wherein Z is hydrogen, sodium or potassium, and where R_2 is PO_3M_2 the reaction is carried out in the presence of a free radical initiator when X and Y together represent a double bond or with the aid of heat when X represents halo and Y is hydrogen;

to form a mercaptan of formula I wherein R_1 is hydrogen, and then optionally:

(2) (a) heating the mercaptan produced in Step (1) with oxygen gas, under pressure, to produce a compound of formula I wherein R_1 is $R_2\text{-}(CH_2)_m\text{-}S\text{-}$ or

(b) reacting the mercaptan produced in Step (1) first with a C_{1-4} alkali metal alkoxide in a protic solvent and then with an alkyl bromide or iodide, to produce a compound of formula I wherein R_1 is C_{1-4}-alkyl.

The process is summarised by the following chart:

$$CH_2 = CH - (CH_2)_n - R_2 \qquad \text{(IIa)}$$

or

$$Hal - CH_2 - CH_2 - (CH_2)_n\ PO_3M_2 \qquad \text{(IIb)}$$

(n = 0, 1 or 2, $R_2 = PO_3M_2$ or SO_3M, M = Na, K or H)

$$\Big\downarrow\ H_2S \text{ or } NaHS \text{ (Step 1)}$$

$$[S - CH_2 - CH_2 - (CH_2)_n - R_2] \qquad \text{(III)}$$

O_2 (Step 2a) → (Ia)

C_{1-4} - alkoxide, Protic solvent, Hal - C_{1-4} - alkyl (Step 2b) → (Ib)

$$\text{(Ia)}\quad \begin{array}{l} S - (CH_2)_m - R_2 \\ | \\ S - (CH_2)_m - R_2 \end{array} \qquad \begin{array}{l} S - (CH_2)_m - R_2 \\ | \\ C_{1-4} - \text{alkyl} \end{array} \quad \text{(Ib)}$$

($m = n + 2$)

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred process of this invention for preparing the compounds of formula I wherein R_1 is R_2-$(CH_2)_m$-S- involves two-steps in a single-pot, which results in the conversion of an alkenyl sulfonate salt or acid ω-alkenesulfonate or -sulfonic acid) to the desired formula I compound, especially dimesna which can be produced thereby in a highly pure form, on a large scale.

Step 1 involves the addition of a sulfhydryl moiety in an anti-Markovnikov fashion to the unsaturated terminal double bond by generating an sp^3 center. The addition to the double bond is effected by reacting the starting alkenyl sulfonate salt with a hydrosulfide salt or with hydrogen sulfide, preferably in a slightly basic

solution (pH from 8 to 9.5). The sulfide is preferably present in at least a stoichiometric proportion and usually in a molar excess of at least 2:1, preferably from 3:1 to 5:1. This step forms a mercapto- (alternatively termed a sulfhydryl-) alkanesulfonate which may be recrystallized directly to produce the compounds of formula I wherein R_2 is hydrogen, especially mesna.

Step 2 of this process, designated step 2(a) above, involves the oxidization of the mercaptoalkanesulfonate to a disulfide and is performed in an aqueous medium and in the same reaction vessel as step 1, without the need to purify or isolate the product of step 1. Step 2 includes the introduction of oxygen gas, preferably by bubbling, into the reaction vessel, along with an increase in pressure and temperature above ambient values, preferably at a slightly basic pH. The preferred pH is from 8 to 9.5. It can remain unadjusted from step 1 which is a big advantage. The preferred temperature is at least 40°, most preferably at least 60°C. A range of 40 to 100°C is contemplated for most purposes. The preferred gauge (superatmospheric) pressure is at least 20psi (138 kPa), more preferably at least 30psi (207 kPa) and most desirably at least 50psi (345kPa). A range of 20 to 60psi (138 to 414kPa) is contemplated for most purposes. Dimesna or a homologue or analogue thereof can be formed in substantially quantitative yield. The desired final product can be easily crystallized from the aqueous reaction medium itself.

If the desired end product is an alkyl thioether of formula I wherein R_1 is C_{1-4} alkyl, step 1 of the process is performed as described above and the mercaptan product is then taken up in a protic solvent, preferably a C_{1-4}-alkanol, which contains a desired C_{1-4}-alkoxide, preferably sodium methoxide. Preferably, the solution is

warmed to about 60°C, followed by the addition of the C_{1-4} alkyl iodide or bromide to effect the alkylation. Preferably the alkyl portion of the alkoxide is the same as that of the alkyl iodide or bromide and even more preferably the protic solvent comprises the corresponding alkanol. The thioether is thus formed in generally quantitative yield.

When a phosphonate of formula I is desired, the starting compound can be a haloalkanephosphate, preferably a bromoalkane- or chloroalkanephosphonate. Preferably n is 0 or 1, the starting material then being a haloethane- or halopropanephosphonate. The two step, single pot process involves first the treatment of this starting compound with sodium hydrosulfide or hydrogen sulfide at elevated temperature, especially from 40 to 120°. The sulfide is preferably used in molar excess, as described above. Alternatively, step 1 may be achieved by converting the alkenephosphonic acid to the mercaptan by addition of a sulfur source, conditions and reagents being as described above, in the presence of a free radical initiator. Step 2, the oxidation to the disulfide, is the same as described above.

The following non-limiting examples illustrate the invention.

EXAMPLE 1

Disodium 2,2'-(dithiobis)ethanesulfonate

100mL of a 25% aqueous stock solution (25 grams VSA, 0.192 mole) of vinylsulfonic acid (VSA) sodium salt (Aldrich Chemical Company) was taken up in a Parr vessel, and argon gas bubbled in for one hour to deoxygenate the aqueous solution. To this solution was added 33.5 grams (0.598 mole, reckoned as NaSH) of sodium hydrosulfide monohydrate (Aldrich Chemical Company) and 10mL of sodium hydroxide. The pH of the solution was approximately 9.0. The reaction mixture was agitated in a Parr apparatus

for two hours, during which time NMR monitoring was conducted at 30 minute intervals.

The product obtained from this step was taken to the next step without isolation, heated to 60°C, and oxygen bubbled into the vessel for thirty minutes. The vessel was then pressurized to 50psi (345kPa) gauge and agitated for six more hours at 60°C.

The completed reaction mixture was then worked up by concentrating the aqueous fraction at 80°C using an industrial vacuum, followed by diffused recrystallization from water. The crystallized product was then lyophilized after adjusting the pH to 7.2 by adding 1N HCl and filtering through a 0.2 micrometre pore membrane filter. NMR and elemental analysis confirmed the presence of pure (99%) sodium 2,2'-(dithiobis)ethanesulfonate.

EXAMPLE 2

Tetrasodium 2,2'-(dithiobis)ethanephosphonate

2-Chloroethanephosphonic acid (1 gram; 6.9 mmoles) was taken up in anhydrous ethanol (10ml) and degassed with a continuous stream of argon for at least 30 minutes. This was then added to a boiling solution of sodium hydrosulfide hydrate (1.4 g, 25 mmol, reckoned as NaSH) in ethanol to obtain a reaction mixture with a final pH of approximately 9. The resultant reaction mixture was then refluxed for 10 hours. The reaction mixture was then cooled and the pH adjusted to 8 using 1N HCl. The solvent was removed and the product was purified by diffused crystallization. The white solid was then taken into a Parr bottle and 50 ml water added. The aqueous solution was then bubbled with a stream of oxygen for a period of at least one hour. Then the bottle was pressurized with 50psi (345kPa) gauge oxygen and shaken at 60°C for 4 hours. The product was isolated

by concentrating the aqueous portion to half at 80°C under industrial vacuum, followed by crystallization. The product thus obtained was then characterized by high field NMR and elemental analysis and by comparing with an authentic sample.

EXAMPLE 3

Tetrasodium 2,2′-(dithiobis)ethanephosphonate

Example 2 was repeated except that the same molar amount of 2-bromoethanephosphonic acid was used as the starting material and the ethanol solvent replaced by water. The title compound thus obtained was then characterized by high field NMR and elemental analysis and by comparing with an authentic sample.

EXAMPLE 4

Monosodium 2-(methylthio)ethanesulfonate

Sodium methoxide (1.5 gram) was taken up in anhydrous methanol (20 ml) and sodium mercaptoethanesulfonate (mesna) (1g) added. The reaction mixture was then refluxed for 6 hours. To the above solution was then added methyl iodide (2ml) and the solution stirred for an additional 2 hours. The reaction mixture was then concentrated and the product was crystallized from water. The title compound, obtained in quantitative yield, was characterized by NMR:

^{1}H NMR (300 MHz, D_2O): 1.99δ (3H, s); 2.67-2.72δ (2H, m); 2.99-3.04δ (2H, m)

^{13}C NMR: δ 13.89, 27.28, 29.92, 50.31

EXAMPLE 5

Monosodium 2-(ethylthio)ethanesulfonate

Example 4 was repeated, substituting the same weights and volumes of sodium ethoxide, ethanol and ethyl iodide for sodium methoxide, methanol and methyl iodide.

The title compound, obtained in quantitative yield, was characterized by NMR:

^{1}H NMR (300 MHz, D_2O): 1.07δ (3H, t, J= 7.5Hz); 2.45δ (2H, q, J= 7.5 Hz); 2.69-2.75δ (2H, m); 2.96-3.02δ (2H, m)

^{13}C NMR: δ 12.65, 23.84, 24.05, 28.96, 49.98

CLAIMS

1. A process for producing compounds of the general formula:

$$R_1\text{-}S\text{-}(CH_2)_m\text{-}R_2; \qquad (I)$$

wherein

R_1 is hydrogen, C_{1-4}-alkyl or $R_2\text{-}(CH_2)_m\text{-}S\text{-}$;

R_2 is SO_3M or PO_3M_2 wherein M or each M independently is sodium, potassium or hydrogen,

and

m is 2, 3 or 4,

said process comprising

(1) reacting a compound of formula

$$CH_2X\text{-}CHY\text{-}(CH_2)_n\text{-}R_2 \qquad (II)$$

wherein

X and Y together complete an olefinic carbon-carbon double bond or, where R_2 is PO_3M_2, X can be halo and Y is then hydrogen;

n is 0, 1 or 2; and

R_2 is as defined above,

with a sulfide of the general formula Z-SH, wherein Z is hydrogen, sodium or potassium, and where R_2 is PO_3M_2 the reaction is carried out in the presence of a free radical initiator when X and Y together represent a double bond or with the aid of heat when X represents halo and Y is hydrogen;

to form a mercaptan of formula I where R_1 is hydrogen, and optionally:

(2) (a) heating the mercaptan produced in step (1) with oxygen gas under pressure, to produce a compound of formula I wherein R_1 is $R_2\text{-}(CH_2)_m\text{-}S\text{-}$ or

(b) reacting the mercaptan produced in step (1) first with a C_{1-4} alkali metal alkoxide in a protic solvent and then with an alkyl bromide or iodide, to produce a compound of formula I wherein R_1 is C_{1-4}-alkyl.

2. A process according to Claim 1, wherein in step (1) the molar ratio of sulfide to compound of formula (2) is in excess of stoichometric.

3. A process according to Claim 1 or 2, wherein in step (2)(a) the pressure is at least 20psi (138kPa) gauge and the reaction is carried out at a temperature of at least 60°C.

4. A process according to Claim 3, wherein in step (2)(a) the pressure is at least 30psi (207kPa) gauge.

5. A process according to Claim 1, 2, 3 or 4, wherein step (2)(a) is carried out to produce a compound of formula I wherein R_1 is $MSO_3-(CH_2)_2-S-$.

6. A process according to Claim 5, wherein the starting compound is a vinyl sulfonate of formula II wherein X and Y together form a double bond, n is 0 and R_2 is SO_3M, the mercaptan reaction product of step (1) is not isolated and step (2)(a) is carried out in the same reaction vessel as for step (1).

7. A process according to Claim 5 or 6, wherein M is sodium and the product is dimesna.

8. A process according to Claim 1, 2, 3 or 4, wherein in step (2)(b) the protic solvent is a C_{1-4} alkanol and the C_{1-4} alkyl moiety of the alkoxide, the alkyl bromide or iodide and the alkanol is the same.

9. A process according to Claim 1, 2, 3, 4 or 8, wherein in step (2)(b) the C_{1-4}-alkyl bromide or iodide is methyl or ethyl bromide or iodide.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C319/04 C07C319/14 C07C319/24 C07C323/66 C07F9/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 5 347 015 A (H.KELLER, ET AL.) 13 September 1994 see the whole document	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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